REMARKS

As a preliminary matter, Applicants would like to thank the Examiner for the courtesy extended during the recent interview. The Office Action dated November 26, 2002 states that the application claims priority to a provisional filed September 10, 1999, however, the provisional priority application was filed September 10, 1998, consistent with the filing receipt for this case.

In view of the above amendments and the following remarks, the Examiner is respectfully requested to withdraw the rejections, and allow claims 1, 8, 14-16, 21, 24-26 and 32-46, the currently pending claims. Claims 1, 24, 35 and 42 have been amended. The amendments to the claims are supported by the specification which states that adenovirus vectors of the invention replicate and/or express an adenoviral gene operably linked to a cell status-specific TRE preferentially in cells whose status permits the function of a cell status-specific TRE (page 10, lines 10-12).

Support for the amending language, "for selective cytolysis of a target cell" may be found in the specification on page 8, lines 19-23 and is further explained on page 9, line 27 through page 10, line 3, wherein the specification states that by providing for cell status-specific transcription of at least one adenovirus gene required for replication, the invention provides adenovirus vectors that can be used for specific cytotoxic effects due to selective replication and/or selective transcription and that this is especially useful in the cancer context, in which targeted cell killing is desirable. See also page 8, lines 19-23 of the specification wherein "cytotoxicity" is defined as cell death and/or cytolysis.

Claims 1, 8, 14-16, 21, 25, 26 and 32-46 have been rejected under 35 U.S.C. 103 as being unpatentable over either one of Henderson *et al.* (WO97/01358); Hallenbeck *et al.* (WO96/17053), Walther *et al.* (Mol. Biotechnol. 6:267-286); Dachs *et al.* (Nat. Med. 3:515-520); Dachs *et al.* (Oncol. Res. 9:313-325); Advani *et al.* (Semin. Oncol. 24:633-638), and Parr *et al.* (Nat. Med. 3:1145-1149). Applicants respectfully submit that the presently claimed invention is not made obvious by the combination of cited references.

The Examiner states that Applicants have described each reference, noted where each reference fails and that the Examiner agrees with Applicants summary of each of the separate references (page 5 of the 11/26/02 Office Action; Paper 28). However, the Examiner argues that the combination of references render the claims obvious. Applicants respectfully disagree. The

claims have been amended to more clearly recite the invention, which is directed to adenovirus vectors "for selective cytolysis of a target cell".

Neither Henderson (WO 97/01358) nor Hallenbeck (WO 96/17053) render obvious replication-competent adenovirus vectors that function in selective lysis of target cells. The specification of the instant case characterizes the adenovirus vectors of the invention as "replication-competent" (page 6, line 2) and states that the invention provides methods of suppressing tumor cell growth comprising contacting a tumor cell with an adenoviral vector of the invention such that the adenoviral vector enters the tumor cell and exhibits selective cytotoxicity for the tumor cell (page 8, lines 19-23).

Further, the prior art is limited to transcriptional regulatory elements that provide for tissue specificity, for example prostate specific expression, liver specific replication, melanoma specific replication, *etc.* The presently claimed invention relates to transcriptional regulatory elements that could be activated in a variety of cell types, and which derive their specificity from the proliferative state of the cell, or the hypoxic state of the cell. It could not have been predicted from the teachings of the prior art that such state-specific elements could provide specificity of replication.

Hallenbeck (WO 96/17053) states that "a general object of the invention is to provide novel vectors for tissue-specific vector replication and gene expression from the replicating vector" and "a further object of the invention is to selectively distribute a vector, a polynucleotide, or a heterologous gene product in a target tissue." (page 6, line 27 through page 7, line 17) Essentially Hallenbeck has made a viral vector into a gene delivery vehicle, and the publication teaches cellular cytotoxicity due to an expressed cytotoxic gene (TK, CD, etc.). Extensive description is provided for direct and indirect toxic effects on target cells (from page 23, line 11 through page 24, line 25), however, the direct killing of cells by the vector itself is not mentioned. In fact, Hallenbeck teaches that replication can be by vector nucleic acid alone or can include virus replication (page 9, lines 18-19), in contrast to the present invention, which requires viral replication and "selective cytolysis".

Although Example 1 of Hallenbeck recites an adenoviral vector with an AFP promoter linked to E1a, and evaluation of virus replication using a plaque assay in A30 cells, Applicants submit that this is a standard means of evaluating viral stocks *in vitro* and one of skill in the art would use such an assay to characterize both replication defective and replication competent viral stocks. Hence, such an assay does not teach or suggest that a vector functions in "selective cytolysis" of particular target cells.

As previously discussed, Henderson (WO 97/01358) describes "adenovirus vehicles" and states that "by providing for regulated transcription restricted to specific host cell targets, one can

provide adenoviruses that can be used as vehicles for introducing genetic capability into host target cells, as distinct from other host cell types. The transgenes serve to modify the genotype or phenotype of the target cell...".

When taken as a whole, Henderson and Hallenbeck teach vectors for replication and delivery of a vector for tissue specific adenovirus expression of a transgene, not cytolysis of target cells based on the proliferative or hypoxic state of the cells. Neither the Hallenbeck nor Henderson references teach or suggest replication competent adenoviral vectors that selectively lyse target cells based on the presence of a hypoxia responsive element or an E2F-1 transcriptional regulatory element as recited by the present claims. In contrast to the prior art, the adenoviral vectors of the present invention do not require the presence of a cytotoxic transgene and rely on the selective replication of the vector itself for cytoxicity to target cells

By way of further support for the nonobviosuness of the present invention, post filing references describe the unexpected advantages offered by the compositions of the present invention. For example, Hernandez-Alcoceba R et al. (Hum Gene Ther 2002 Sep 20;13(14):1737-50) describe oncolytic adenoviruses with hypoxia- and estrogen receptor-regulated replication. One exemplary virus has the E2F-1 promoter (AdEHE2F) incorporated into the E4 region of the human adenovirus type 5 genome, together with expression of the adenoviral E1A gene (which is essential for replication) controlled by a minimal dual-specificity promoter such that replication occurs in response to estrogens and hypoxia. The reference demonstrates the surprising cancer cell specificity, and selective cytolysis, that can be achieved with a replication competent adenovirus comprising a hypoxia responsive element (HRE) operably linked to an adenovirus gene essential for replication, as set forth in the present claims.

Tsukuda et al. (Cancer Res. 62:3238-3447, 2002), describe regulation of adenovirus replication in tumor cells based on a vector wherein the E1A gene is operably linked to the E2F promoter resulting in E2F-regulated expression of E1-deleted adenovirus. The control of E1A by an E2F responsive promoter allowed for selective replication of the adenovirus in tumor cells, providing significant *in vivo* therapeutic benefit. Johnson *et al.* (Cancer Cell 1:325-337, 2002), describes an oncolytic virus construct, ONYX 411, which has a deletion in the E1A-CR2 region and exhibits E2F-regulated expression based on the E1A or E4 gene under operative control of the E2F-1 promoter. The report discloses that the adenovirus had a cell killing capacity comparable to wild-type adenovirus in a variety of tumor cells, but was markedly attenuated in the killing of normal cells.

In contrast to the presently claimed invention, the AFP promoter exemplified in Hallenbeck is not cancer cell specific. See, e.g., Huber BE et al. (Hepatology 1986 Mar-Apr;6(2):209-19) which teaches that a quantitative increase in AFP transcription and translation occurs in regenerating rat

liver, and Geissler M et al. (Gastroenterology 2001 Oct;121(4):931-9), which shows that liver regeneration in humans and mice is associated with increased AFP expression and that administration of DNA encoding mouse AFP to mice resulted in significant hepatocyte damage to regenerating liver. The lack of specificity of the AFP promoter suggests that vectors wherein replication is regulated by an AFP promoter linked to E1a alone are not effective for selective cytolysis of cancer cells.

The Walther *et al.*, Dachs *et al.*, Dachs *et al*, Advani *et al.* and Parr *et al.* references describe various cell status regulatory elements that are useful in gene delivery vehicles. In other words, the secondary references merely describe particular regulatory elements and this disclosure does not compensate for the lack of teaching in Henderson (WO 97/01358) and Hallenbeck (WO 96/17053) relative to replication-competent" adenoviral vectors that exhibits selective cytotoxicity for a cell based on the state of the cell. Thus one of skill in the art would not arrive at the claimed invention if the cited references were to be combined and the combined references do not provide a reasonable expectation of success in practicing the present invention.

Applicants respectfully submit that the presently claimed invention meets the requirements of 35 U.S.C. 103. In view of the above remarks, withdrawal of the rejection is requested.

CONCLUSION

Applicants submit that all of the claims are now in condition for allowance, which action is requested.

The Commissioner is hereby authorized to charge any other fees under 37 C.F.R. §§ 1.16 and 1.17 which may be required by this paper, or to credit any overpayment, to Deposit Account No. 50-0815, order number CELL-014.

Respectfully submitted,

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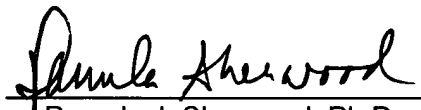
By: 
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